PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P66981	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/014102	International filing date *(day/month/year)* 10.12.2004	Priority date *(day/month/year)* 16.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07C213/08 C07C217/74		
Applicant KRKA, TOVARNA ZDRAVIL, D.D. NOVO MEST et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.07.2005	27.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Zervas, B Telephone No. +31 70 340-3667

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/014102

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-8 received on 20.12.2005 with letter of 16.12.2005

   Claims, Numbers

   1-26 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☒ the claims, Nos. 9-26
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/014102

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: WO 02/45658 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; DOL) 13 June 2002 (2002-06-13)

1. Novelty

The present application does meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 8 is new in the sense of Article 33(2) PCT.

The subject-matter of claim 1 and dependent claims 2 - 8 is novel, because the prior art does not disclose a process for preparing venlafaxine which comprises the conversion of a venlafaxine precursor in the presence of a salt of formic acid wherein the molar ratio of the salt of formic acid to the venlafaxine precursor is 0.3-10 to 1.

2. Inventive Step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 8 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as representing the closest prior art. D1 discloses the preparation of venlafaxine from a venlafaxine precursor in the presence of a salt of formic acid wherein the molar ratio of the salt of formic acid to the venlafaxine precursor is 0.1 to

1. In view of D1 the problem underlying the present application is defined as providing an alternative process for the preparation of venlafaxine. To solve this problem the Applicant provides the process of the present application which differs from the prior art process in that the amount of formic acid salt in relation to the venlafaxine precursor is higher. However, such a modification of the reaction parameters is regarded as common practice for the person skilled in the art and does consequently not involve an inventive step. An inventive step could only be acknowledged if the Applicant could verify unexpected effects resulting from such a modification of a parameter e.g. by means of a

convincing comparative test, thus a comparative test in which the only difference between the examples and the comparative example is the modified parameter. However, no such convincing results are given in the present application.

3. Industrial Applicability

The process of the present application is industrial applicable. It can be used to prepare the drug venlafaxine.

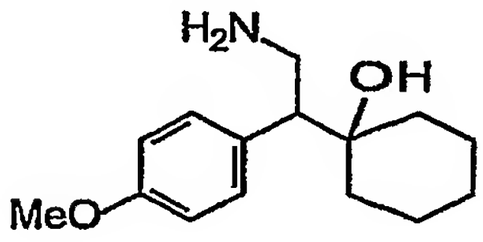
4. Remark

The description should have been adapted to the amended set of claims.

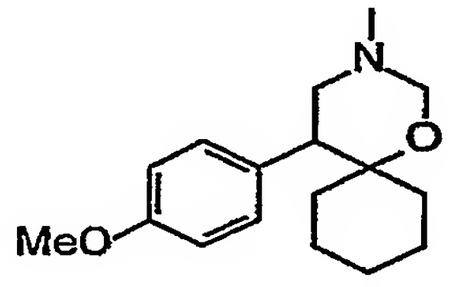
CLAIMS

1. Process for preparing venlafaxine which comprises

(a) converting a venlafaxine precursors selected from the group of *N,N*-didesmethyl venlafaxine of formula (I), a salt thereof, spiro venlafaxine of formula (II) and a salt thereof



(I)



(II)

to venlafaxine, wherein the conversion is carried out in the presence of a salt of formic acid which is selected from the group of a metal salt or an ammonium salt of formic acid, and [—], and

(b) optionally reacting the venlafaxine with an acid to prepare an acid addition salt of venlafaxine.

~~2. Process according to claim 1,~~ [wherein the molar ratio of the salt of formic acid to the venlafaxine precursor is

0.3-10 to 1

2. Process according to claim 1, wherein the molar ratio is 0.5-3 to 1.

3. Process according to ~~any one of~~ claims 1 or 2 ~~to 3~~, wherein the metal salt of formic acid is an alkali or earth alkaline metal salt of formic acid.

4. Process according to claim 3, wherein the alkali metal salt of formic acid is a Na, K or Li salt.

5. Process according to any one of claims 1 to 4, wherein in step (a) *N,N*-didesmethyl venlafaxine (I) or a salt thereof is converted to venlafaxine in the presence of formaldehyde and formic acid .

6. Process according to claim 5, wherein in step (a) the *N,N*-didesmethyl venlafaxine (I) is used in form of its HCl addition salt.

7. Process according to claim 5 or 6, wherein in step (a) the conversion is effected in the presence of also an alkali metal or earth alkaline metal hydroxide or NH_4OH in such an amount that it forms in-situ the salt of formic acid.

8. Process according to claim 7, wherein the alkali metal hydroxide is NaOH which forms in-situ Na formiate.

AMENDED SHEET